PATENT
Attorney Docket No. EPX-006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S):	Dhanoa et al.	GROUP NUMBER:	1624
APPLICATION NO:	10/768,579	EXAMINER:	Emily B. Bernhardt
TITLE:	NEW ARYLPIPERAZINYL COMPOUNDS		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

Please note that the content of this Information Disclosure Statement is substantially the same as that filed by Applicants on July 21, 2006, *e.g.,* prior to the filing of the present Request for Continued Examination. Applicants respectfully request consideration of this Information Disclosure Statement, which was previously found to be not proper for consideration in the office communication dated August 10, 2006.

In accordance with the provisions of 37 C.F.R. 1.97(d) and 1.98, Applicants hereby make of record the items of information listed on the accompanying Form PTO-1449, for consideration by the Examiner in connection with the examination of the above-identified patent application. Submission of these items of information is motivated by very unusual circumstances as set forth below.

On or about Friday, July 14, 2006, a scientist employed by Predix Pharmaceuticals Holdings Inc., the assignee of this application, became aware of publicly available message board postings on the Yahoo! Finance Stock Message Board for Epix Pharmaceuticals Inc. (http://finance.yahoo.com/q/mb?s=EPIX) authored by a Mr. Daniel A. Pearson under the alias "Iron2_2000" that was critical of this application. This item of information is **C1** in the enclosed

PTO-1449 form. This was mildly upsetting to Applicants, as Predix relies on this application for patent protection of a compound currently in Phase III clinical studies. Also, because Predix was in the midst of a merger transaction with Epix Pharmaceuticals, a public company, which is subject to Epix stockholder approval, Predix suspected that Mr. Pearson's motivation in posting these comments was to attempt to influence that vote. (The merger has since been completed.) Nothing in these comments presented any facts or information Applicants or the undersigned regarded as material to examination, and had Mr. Pearson's efforts ended there, the matter likely would have ended. However, after Mr. Pearson learned through public sources that the application had been allowed on July 11, 2006, he sent the undersigned (submitted as item **C2** in the enclosed PTO-1449 form) a letter and a copy of Journal of Medicinal Chemistry, *J. Med Chem* **2001**, *44* 198-207, López-Rodríguez et al., which was available more than a year prior to the filing date of this application. The letter refers to a publication authored by Predix scientists Becker et al (*J. Med Chem* **2006**, *49* 3116-3135, a copy of which is enclosed for convenience). Mr. Pearson argued in his correspondence that these publications negate patentability of the allowed claims, and insinuated that they had been intentionally withheld by the inventors in violation of their duty to disclose information material to patentability.

Some investigation quickly revealed that Mr. Pearson is a former, likely disgruntled employee of Epix, that he is a registered patent agent (Reg. No. 58,053), and that he had recently been posting various accusations concerning this application. He clearly waited to address his allegations to the undersigned until after allowance of this application, at a time he knew Patent Office rules make it difficult for Applicants to have the art considered by the Examiner. We believe Mr. Pearson hopes Applicants would not cite his proffered information, thereby setting up a future allegation of inequitable conduct in litigation, or would abandon the application in favor of a continuation in order to get the art considered, thus frustrating Predix' ability to report to the public a significant positive event before the merger vote.

Of course, the undersigned immediately investigated the merits of his arguments, reviewed the cited papers, reviewed the content of the prosecution in this application, and conferred with the Applicants. As a result of this work, he concluded that the art was at best

cumulative of prior art documents of record provided to the Examiner and to information found in the Examiner's chemical structure searching during prosecution of this application, and as such in his judgment were not material to patentability (a discussion of this issue is set forth below).

However, Applicants wish to have independent Patent Office confirmation (or refutation) of this conclusion by consideration of this Information Disclosure Statement. For that purpose, Applicants request that the Examiner independently consider whether the Pearson papers raise an issue of patentability so that the references and other attached material can be made of record, and if she finds, contrary to Applicants' belief, that this information raises an issue of patentability, permit Applicants to respond to her findings.

As noted by the authors of the '06 paper, a series of studies by López-Rodríguez (one of which is recounted in the Pearson-cited '01 paper) used extensive SAR analysis together with 3D-QSAR models to characterize a range of arylpiperazines, mainly bicyclohydantoin or diketopiperazine analogs. The López-Rodríguez studies state that the pharmacophore part of their molecules is in the pyrimidinepiperazine or arylpiperazine segment, while the rest of the molecule is nonpharmacophoric (*see, e.g., J. Med Chem* **2001**, *44* 186-197). However, other prior art documents of record herein that recognize the promise of arylpiperazines as 5-HT_{1A} receptor ligands include Bojarski et al. 2002 and Rasmussen et al. 2000 cited by Applicants. Applicants believe there are many such papers, probably hundreds. These same studies at the same time show (as is well known in the art – see the Oh et al. article discussed below) that many such compounds exhibit high levels of undesirable affinity to the $\alpha 1$ adrenergic receptor; and that it is very difficult to engineer potent compounds that are selective to one or the other, although examples of selective 5-HT_{1A} binders have been reported. *The López-Rodríguez et al. paper neither discloses nor suggests the compounds falling within any of the allowed claims of this application.* Furthermore, as noted in more detail below, similar compounds, and compounds arguably closer in structure to the compounds disclosed in the López-Rodríguez et al. paper, were specifically considered during examination of this application.

Mr. Pearson argues that the López-Rodríguez '01 paper describes a "solution" to 5-HT_{1A} selectivity – "a meta amide or sulfonamide substituent on the aryl ring of the arylpiperazine moiety" and insinuates that Applicants are proffering the same solution. However, this statement ignores that none of Applicants' allowed claims permit the tetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione ring structure required by López-Rodríguez et al. It is thus without scientific or logical merit that the "solution" described in the '01 paper is some singular magic bullet to the issue of 5-HT_{1A} compound selectivity.

The Oh et al. review, cited by Applicants and of record in the current case, lays this argument to rest. Oh et al. is a detailed review of the status of research on serotonin receptors and transporter ligands as of 2001, and the López-Rodríguez et al. published work is well represented. 5-HT_{1A} receptor ligands are discussed in-depth on pp. 1000-1007. The arylpiperazine pharmacophore appears on the first page of the article. The López-Rodríguez papers are cited on page 1000 [Refs 15, 16] and discussed in detail on page 1004 [Refs 22, 23]. Figures 14, 15 and 16 on page 1004 show the structures of the López-Rodríguez compounds and also discuss the many ways other laboratories have tried to obtain selective 5-HT_{1A} compounds. The many compounds discussed include selective 5-HT_{1A} compounds featuring, in the "non-pharmacophoric" portion of the molecule: a tetralin group (*see, e.g.,* compounds 17 and 18); a bidentate ligand (compound 85); and a fluorochroman group (compound 63). While described in the review as selective, none of these compound feature the selectivity "solution" urged by Mr. Pearson, and as far as Applicants are aware, none have been successful clinically.

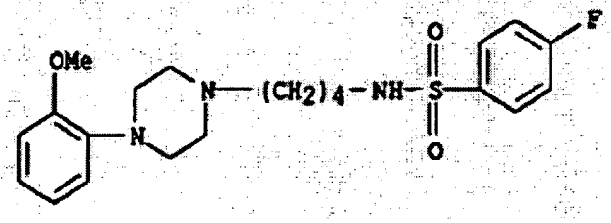
The "inequitable conduct" charge tossed out in the message board posts also is meritless.[1] As noted above, the findings of López-Rodríguez are well-presented in the Oh et al. review. Applicants, who are very familiar with the work in this field, and with the López-Rodríguez work, properly considered citation of the '01 paper *in addition to* the Oh et al. article and numerous other more pertinent references to be cumulative to art considered in examination.

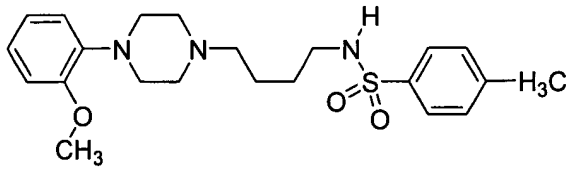
[1] Mr. Pearson, in a communication cited in the attached PTO-1449 and sent to Applicants on August 15, 2006 (after the Information Disclosure Statement became posted on PAIR) denies that he is neither "... someone who would set up a situation in which a future allegation of inequitable conduct could be made" nor "a former, likely disgruntled employee of Epix". This communication is included herewith as document **C3**.

Turning to the email communication, Mr. Pearson asserts that a compound discussed in the Becker et al. paper, N-(4-(4-(2-methoxy-phenyl)-piperazin-1-yl)-butyl)-4-methyl-benzenesulfonamide (the "N-4-4" compound), was not disclosed to the USPTO and insinuates that the omission of this, taken with the alleged importance of the López-Rodríguez '01 paper was material because "(g)iven López in view of the disclosure of the ... compound used as a starting point in the Predix invention, a person skilled in the art may have been motivated to prepare the compound recited by claim 35 or other compounds recited by the claims of the '579 application at the time these inventions were made".

Applicants submit this also is without merit. First, the "N-4-4" compound was a starting point for the making of the invention, and is not claimed herein. Furthermore, the Examiner, in her search, found a plethora of compounds similar to the "N-4-4" compound. For example, the "N-4-4" compound differs from a compound found in the Examiner's search (CA RN 869383-35-7) by only the presence of a fluorine atom (instead of a methoxy group in the above compound.) (see below for comparison).

RN 869383-35-7 CAPLUS
CN Benzenesulfonamide, 4-fluoro-N-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl]- (9CI) (CA INDEX NAME)





It is clear that the "N-4-4" compound is no more relevant than the many other compounds of record in the current file. Furthermore, it is axiomatic that patentability "shall not be negatived by the manner in which the invention was made" (35 USC §103(a)). As such, the structure of this starting compound does nothing to support the specious argument advanced by

Mr. Pearson. More importantly, the Examiner clearly considered that the allowed claims were patentable over compounds such as CA 869383-35-7 in view of the teachings of the art of record.

In accordance with the provisions of 37 C.F.R. 1.97, this statement is being filed (CHECK ONE):

☒ (1) within three (3) months of the **filing date** of a national application other than a continued prosecution application under 37 C.F.R. 1.53(d), or within three (3) months of the **date of entry of the national stage** as set forth in 37 C.F.R. 1.491 in an international application, or before the mailing of the **first Office action** on the merits, or before the mailing of a **first Office action** after the filing of a request for continued examination under 37 C.F.R. 1.114; or

☐ (2) after the period defined in (1) but before the mailing date of a **final action** or a **notice of allowance** under 37 C.F.R. 1.311, and
the requisite Statement is below, **OR**

☐ (3) the requisite fee under 37 C.F.R. 1.17(p), namely **$180.00**, is included herein, or
after the mailing date of a **final action** or **notice of allowance** but before the payment of the **issue fee**, **AND**
the requisite Statement is below, **AND**
the Commissioner is hereby authorized to charge $180, the requisite petition fee under 37 C.F.R. 1.17(p), namely **$180.00**, to **Deposit Account No. 07-1700, Reference PRE-006.**

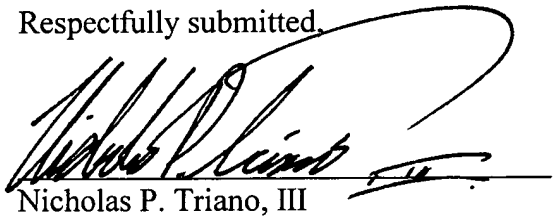
STATEMENT

As required under 37 C.F.R. 1.97(e), Applicants, through the undersigned, hereby state either that **[check the appropriate space only if either (2) or (3) is checked on the previous page and the Statement is required]**:

1. Each item of information contained in the Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application **not more than three months** prior to the filing of the Information Disclosure Statement; or

2. No item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing this Statement after making reasonable inquiry, no item of information contained in the Information Disclosure Statement was known to **any individual** designated in 37 C.F.R. 1.56(c) **more than three months** prior to the filing of the Information Disclosure Statement.

Respectfully submitted,



Date: September 5, 2006
Reg. No. 36,397

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PTO/SB/92 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
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Application No. (if known): 10/768,579 Attorney Docket No.: EPX-006

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on September 5, 2006 .
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Teresa Barbuto
Typed or printed name of person signing Certificate

Registration Number, if applicable

(617) 570-1000
Telephone Number

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

Information Disclosure Statement (7 pages); Form 1449 (1 page); References C1 – C3; Request for Continued Examination Transmittal (in duplicate)(2 pages); and a Return Receipt Postcard.

FORM PTO - 1449 INFORMATION DISCLOSURE STATEMENT	ATTORNEY DOCKET NO.: EPX-006 APPLICANTS: Dhanoa et al. SERIAL NO.: 10/768,579 FILING DATE: January 30, 2004 GROUP: 1624

U.S. PATENT DOCUMENTS

EXAM. INIT.		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPROPRIATE
	A1						

FOREIGN PATENT DOCUMENTS

EXAM. INIT.		DOCUMENT NUMBER	DATE	COUNTRY CODE	CLASS	SUB CLASS	FILING DATE	ABSTRACT ONLY	ENGLISH LANG (Y/N)
	B1								

EXAMINER	DATE CONSIDERED

EXAM. INIT.		OTHER DOCUMENTS: (Including Author, Title, Date, Relevant Pages, Place of Publication)
	C1	Daniel A. Pearson message board postings on the Yahoo! Finance Stock Message Board for Epix Pharmaceuticals Inc. authored by Mr. Daniel A. Pearson under the alias "Iron2_2000" http://finance.yahoo.com/q/mb?s=EPIX
	C2	Email from Daniel A. Pearson to Attorney Nicholas P. Triano III, dated July 15, 2006, with enclosures (email letter and *J. Med Chem* **2001**, *44* 198-207)
	C3	Email letter from Daniel A. Pearson to Attorney Nicholas P. Triano III, dated August 15, 2006
	C4	
	C5	
	C6	

EXAMINER	DATE CONSIDERED